

### **DETAILED ACTION**

This Office action VACATES the previous Office action mailed 4/21/2008.

Upon further consideration, the Finality of the Office action mailed 7/27/2007 is Withdrawn, and prosecution on the merits continues.

The after-final amendment filed 10/29/2007 is acknowledged and has been entered.

Claims 21, 22, 24, 25, and 27-32 are pending. Claim 21, 22 and 27, drawn to non-elected inventions, are withdrawn from consideration. Claims 24, 25 and 28-32 are examined on the merits.

#### ***Priority***

A certified copy of Priority document JP 2003-038643 is present in the file.

#### ***Claim Rejections Withdrawn:***

The rejection of claims 13, 23-26 and 28-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

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The rejection of claims 13, 23-26 and 28-32 under 35 U.S.C. 112, first paragraph, because the specification for lack of enablement of the full scope of the claims, is withdrawn in view of the amendment to the claims.

The rejection of claims 13 and 23 under 35 U.S.C. 102(b) as being anticipated by Kipriyanov (Kipriyanov, G. et al., Protein Engineering, 10(4): 445-453, 1997) is withdrawn in view of the amendment.

***New Grounds of Rejection:***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 24, 25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abstract 3P-214 (Asano, R., et al, 75<sup>th</sup> Annual Congress of The Japanese Biochemical Society, 74(8): August 25, 2002; cited in the IDS; English translation provided) in view of Adair (Adair, J. R. et al, Human Antibodies Hybridomas, 5: 41-47, 1994; cited in IDS), in view of Gill (Gill, G.N. et al., The Journal of Biological Chemistry, 259(12): 7755-7760, 1984) and further in view of Wu (Wu, H. et al., J. Mol. Biol., 294: 151-162, 1999).**

The inventorship of appears to be different from that of the instant invention, because for abstract #3P-214 there are 5 authors, whereas the instant application names 4 inventors. Therefore, abstract 3P-214 appears to be "by another".

Claims 28 and 29 are drawn to humanized diabody-type bispecific antibodies comprising 2 polypeptide chains, where the first polypeptide chain comprises SEQ ID NO: 43 and SEQ ID NO: 46, and the second polypeptide chain comprises SEQ ID NO: 44 and SEQ ID NO: 45. The amino acid sequence of SEQ ID NO: 44 is the amino acid sequence of the variable region of the light chain of Adair's humanized OKT3 antibody, and the amino acid sequence of SEQ ID NO: 43 is amino acid sequence of the variable region of the heavy chain of Adair's humanized OKT3 antibody (specification teaches that that the humanized OKT3 antibody of Adair was used to

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make the anti-CD3 binding site of the claimed bispecific antibodies; see page 28, Example 11).

The amino acid sequence of SEQ ID NO: 46 is the amino acid sequence of the variable region of the light chain of a humanized 528 anti-EGFR antibody, and the amino acid sequence of SEQ ID NO: 45 is the amino acid sequence of the variable region of the heavy chain of a humanized 528 anti-EGFR antibody. Within the scope of the claims is a species of diabody, where one part of the diabody is provided by the prior art (humanized OKT3) and the other part of the diabody is humanization by direct CDR grafting of a known anti-EGFR antibody (528 antibody). Claims 24 and 25 are drawn to pharmaceutical compositions comprising the diabody of claim 28. The phrase “pharmaceutical composition” is interpreted as an intended use of the product comprised within the pharmaceutical composition.

Abstract #3P-214 teaches the Ex3 bispecific diabody and teaches that it is a diabody made from the anti-EGFR 528 heavy and light chains together with the heavy and light chains of the OKT3 antibody. Abstract #3P-214 fails to teach a humanized version of the Ex3 diabody.

However, the humanized version of OKT3 antibody was known in the art at the time the invention was made as evidenced by the teachings of Adair. Further, the 528 antibody was known in the art as were methods for humanizing antibodies, as evidenced by the teachings of Gill and Wu, respectively. Since within the scope of the claims is a species where for the anti-EGFR part of the diabody simply CDR swapping was performed, and because CDR swapping is one of the first steps in humanizing an antibody (see Wu, page 152, 1st and second column, and page 157, 2nd column, and page 158, 2nd column), it would have been prima facie obvious to one of skill in the art at the time the invention was made to have humanized the Ex3 antibody taught by Abstract #3P-214 by using the art known humanized OKT3 antibody of Adair together

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with a humanized form of the art-known 528 anti-EGFR antibody. One would have been motivated to have humanized the Ex3 antibody because its intended use is for human therapy, and humanization of antibodies is known to decrease the antigenicity of non-human antibodies (See Wu, page 152, 1<sup>st</sup> column).

***Additional references considered:***

Hayashi, Hiroki, et al., The 61<sup>st</sup> General Meeting of Japanese Cancer Association Presentation, Abstract #2125, October 1, 2002. An English-language translation of this document was considered and not applied as prior art because the disclosure merely named the binding specificity of the two arms of the bispecific antibody, and did not disclose a structure or the source of the parent antibodies.

***Conclusion***

No claim is allowed.

Claims 30-32 are objected to for depending from a rejected claim. Claims 24, 25, 28 and 29 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry

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Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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April 14, 2008  
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